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ARTICLE TYPE

Asymmetric Addition of Chiral Boron-Ate Complexes to Cyclic Imminium Ions

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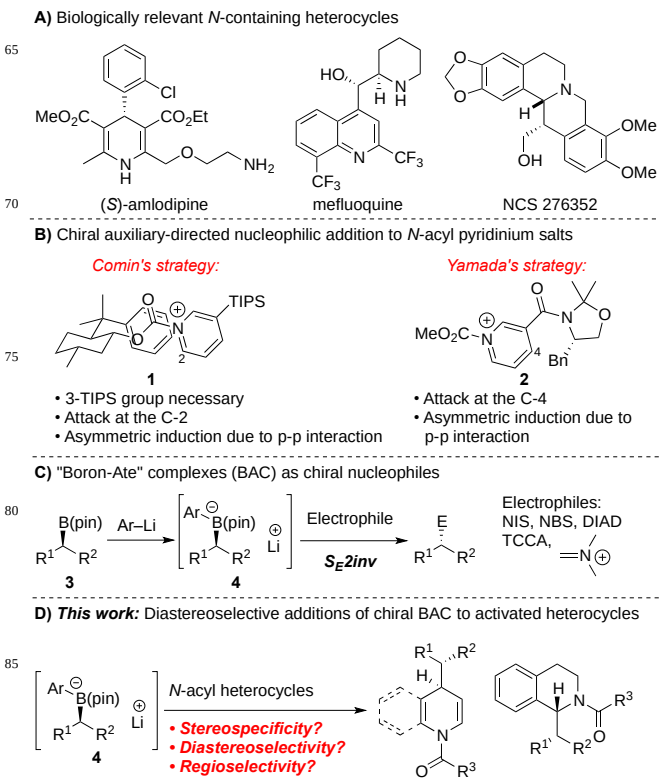
Boronate complexes derived from enantioenriched secondary benzylic boronic esters and aryl lithiums have been reacted with quinolinium, pyridinium and dihydroisoquinolinium salts to give enantioenriched heterocyclic structures with very high diastereocontrol over two contiguous stereogenic centres (87:13-99:1 dr; >95:5 es). The salts were derived from the corresponding heterocycle and Troc-Cl or dimethylTroc-Cl. In the case of the quinolinium, and pyridinium salts the presence of a 3-carboxyamide group increased both reactivity and diastereoselectivity. The unusually high diastereoselectivity observed is thought to originate from strong cation-π interactions between the cationic heterocycle and the electron rich benzylic boronate complex with minimisation of steric interactions between the substituents on the ate complex and the non-planar substituents on the heterocycle.

Introduction

Nitrogen-containing heterocycles are common motifs in natural products, and are privileged structures in pharmaceutical and agrochemical products, as well as in materials science (Scheme 1A).[1] Easy access to non-aromatic (3-D) heterocycles is a major contemporary goal especially in the pharmaceutical industry, as many of the chemical libraries tested previously have taken advantage of the Suzuki cross-coupling reaction which have led to flat (achiral) molecules, with limited success in terms of activity. Indeed, it has been shown that molecular descriptors such as the fraction of sp^3 carbon atoms and the numbers of stereocentres in a molecule correlate with clinical success.[2] Nucleophilic addition to aromatic (flat) pyridines, quinolines and isoquinolines provides a simple strategy to access 3-D-heterocycles.[3] However, the development of asymmetric processes is particularly challenging due to (i) poor regioselectivity and (ii) poor stereocontrol due to low face discrimination by the nucleophile.[3] Currently, the most effective solutions utilize chiral auxiliaries to achieve diastereoselective additions to pyridinium salts. Comins'[4] and Yamada's[5] systems **1** and **2** represent the state-of-the-art and afford [1,2] and [1,4] additions of carbon nucleophiles to pyridinium salts respectively (Scheme 1B).[6] In the cases of quinolinium-[7] or (dihydro)isoquinolinium-based[8] scaffolds few asymmetric additions are known. Thus, general and efficient methods for the synthesis of these scaffolds with high regio- and stereocontrol are highly desirable.

We have recently developed a new class of configurationally stable chiral nucleophiles based on chiral boronic esters, and have shown that they react with a broad range of electrophiles with complete (in many cases) inversion of configuration (S_E2inv) (Scheme 1C).[9] These new reagents are easily formed by the addition of an aryllithium to an enantioenriched secondary pinacol boronic ester **3**, thus producing the nucleophilic "boron-ate" complex (BAC) **4**, which transfers its chiral organic component with high stereospecificity to the electrophilic partner. Based on this, we envisioned that cationic quinolinium, pyridinium and dihydroisoquinolinium salts would react with this new and promising class of chiral nucleophiles, thus providing a novel and attractive method for the synthesis of chiral heterocyclic scaffolds bearing two adjacent stereogenic centres (Scheme 1D).[10]



Scheme 1.

Herein we describe our success in developing a highly regio- and (surprisingly) highly diastereoselective addition of boron-based nucleophiles to such heterocycles with complete stereospecificity. To the best of our knowledge, transformations of this type have not been generalized in any previous format and should be of general utility for the synthesis of both natural products and biologically active compounds.

Design Plan

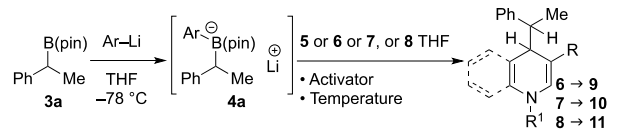
In accordance with our previous studies, we expected our BACs to be reactive enough to undergo additions to *N*-activated heterocycles but significant issues needed to be addressed. Since both C-2 and C-4 of quinolines and pyridines are activated, regio-control is an issue.[11] In addition, our chiral nucleophiles had to further discriminate between the two diastereotopic faces of the aromatic electrophiles. Despite these challenges and the lack of precedent in this area, we embarked on this project. At this stage we decided to employ *N*-acyl instead of *N*-alkyl iminium ions due to their increased reactivity and stability.[3]

Results and Discussion

Additions to Quinolines and Pyridines – Reaction Optimisation and Substrate Scope

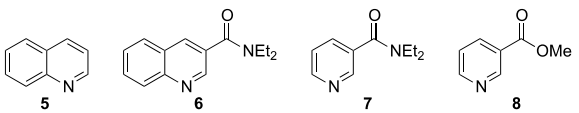
To evaluate the efficiency of this new process, we started our investigation by using the readily available benzylic boronic ester **3a** as a proto-nucleophile. Thus, after formation of the corresponding BAC **4a**[12] by addition of *p*-MeO-Ar–Li at –78 °C, the mixture was warmed to rt and isoquinoline **5** and acetyl chloride were added. As shown in Table 2, these initial reaction conditions gave the 1,4-addition product exclusively, albeit in modest yield (entry 1). This high regioselectivity is believed to be due to steric interactions between the large nucleophile and the activating group on nitrogen. Changing the activator to the more reactive chloroformates gave slightly improved yields (up to 40% using 2,2,2-trichloroethyl chloroformate – TrocCl) but with poor diastereoselectivity (*anti*:*syn* 60:40) (for the diastereomeric assignment, *vide infra*). As might be expected, reducing the reaction to –78 °C provided a modest increase in the diastereoselectivity but gave an increased yield of 72% (entry 6). The improved levels of induction and efficiency prompted us to evaluate different substrates. We reasoned that the presence of a carbonyl-based group on the *C*-3 of the quinoline ring would be beneficial on the basis of two synergistic effects. We speculated that it would (i) further activate the *C*-4 position towards nucleophilic attack but more importantly (ii) increase the steric interactions between the reactants during the nucleophilic attack. We were particularly inspired by Yamada's crystallographic evidence which showed that a diethyl amide functionality [C(O)NEt$_2$] adopted an orientation in which it was perpendicular to the aromatic ring of a pyridine, where it suffered less steric hindrance, rather than co-planar where it might gain electronic stabilisation through delocalisation.[5] Thus, when quinoline **6** was tested, the desired product was obtained in a moderate 36% yield but a remarkably high 94:6 dr (*anti*:*syn*) (entry 6). We then explored alternative Ar–Li reagents particularly as we had previously found that the use of the 3,5-(CF$_3$)$_2$Ar group was sometimes beneficial.[9] Thus, when 3,5-(CF$_3$)$_2$Ar–Li was used to generate the required BAC, the reaction with **6** and TrocCl gave the addition product in 65% yield and 98:2 dr. With these reaction conditions in hand we evaluated the use of the more challenging pyridine **7**.[13] In this case, the optimum reaction temperature was found to be –40 °C (entry 9 and 10). Also in this case, the presence of an electron deficient aromatic group in the BAC was beneficial and the desired dihydropyridine was formed in 83% yield and 94:6 dr (*syn*:*anti*) (entry 11).[14] The use of 3-carbomethoxy substituted pyridine **8** was also evaluated but in this case the desired addition product was obtained in slightly lower dr (entry 12).[15] To the best of our knowledge, such levels of face-selectivity for the addition of either chiral or achiral nucleophiles to pyridinium ions are unprecedented without the use of chiral auxiliaries attached to the heterocyclic scaffold.

Table 1.



Entry	*N*-Het	Ar–Li	Activator	T (°C)	Yield (%)[a]	dr (*syn*:*anti*)[b]
1	**5**	*p*-OMePh–Li	AcCl	rt	33	–
2	**5**	*p*-OMePh–Li	CbzCl	rt	35	–
3	**5**	*p*-OMePh–Li	EtOC(O)Cl	rt	35	63:37
4	**5**	*p*-OMePh–Li	PhOC(O)Cl	rt	38	61:39
5	**5**	*p*-OMePh–Li	TrocCl	rt	40	60:40
6	**5**	*p*-OMePh–Li	TrocCl	–78	72	75:25
7	**6**	*p*-OMePh–Li	TrocCl	–78	36	94:6
8	**6**	3,5-(CF$_3$)$_2$Ph–Li	TrocCl	–78	65	98:2
9	**7**	*p*-OMePh–Li	TrocCl	–20	33	91:9
10	**7**	*p*-OMePh–Li	TrocCl	–40	38	92:8
11[c]	**7**	3,5-(CF$_3$)$_2$Ph–Li	TrocCl	–40	83	94:6
12[c]	**8**	3,5-(CF$_3$)$_2$Ph–Li	TrocCl	–40	83	89:11

a) Yields after column chromatography. b) Determined by ^{1}H NMR spectroscopy and chiral HPLC on the crude. c) The final concentration was 0.3M.

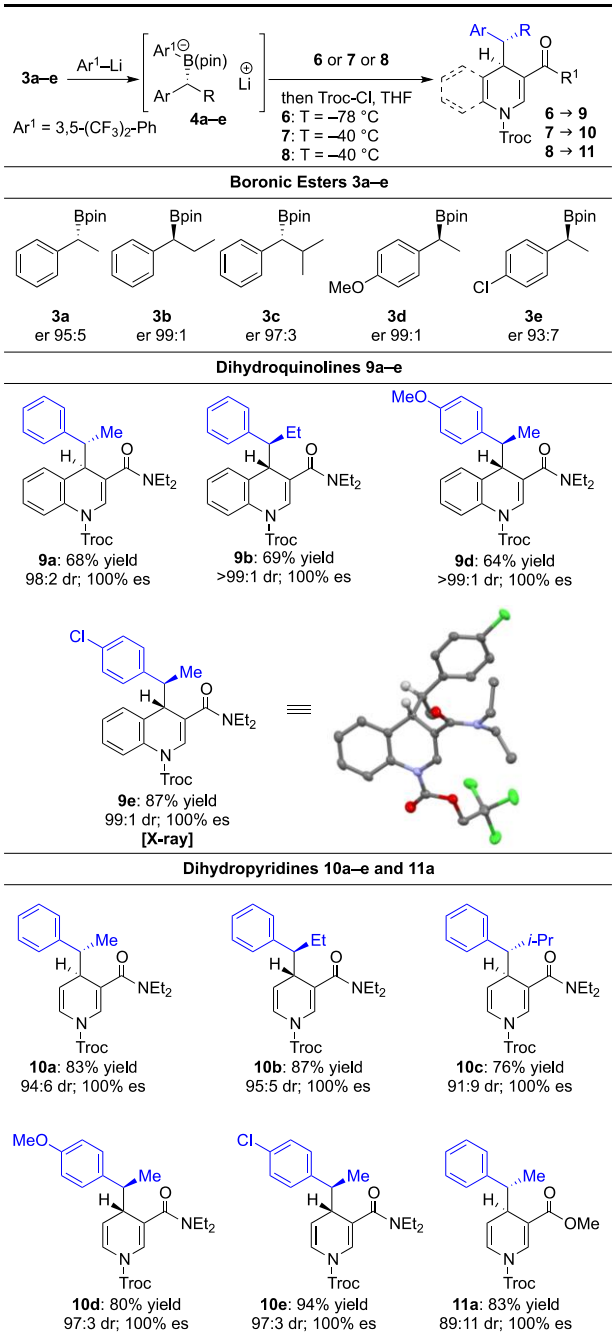


A key aspect in the chemistry of chiral nucleophiles is represented by the reaction stereospecificity. This aspect might become particularly problematic if a combination of ionic (S_E2inv in our case) and radical (SET) pathways participate simultaneously.[9] Determining the enantiospecificity of the reaction was thus deemed necessary to establish our new protocol.

We were pleased to find that the reaction with enantioenriched boronic ester **3a** [er (*R*:*S*) 95:5][16] delivered **9a** in identical yield and diastereoselectivity whereby the main diastereomer was also formed with 100% enantiospecificity (es) thus excluding the possible intermediacy of SET processes (Table 2). With this simple procedure in hand, a range of different chiral boronic esters was evaluated with the 3-substituted quinoline **6** and the pyridine **7**. Gratifyingly, the nucleophilic additions to **6** proceeded in very good yields with excellent levels of

diastereoselectivity (>99:1) and complete es (100%). This is the first example of a highly diastereoselective 1,4-addition to quinolines. Compound **9e** was crystallised from Et_2O/pentane providing good quality crystals for X-ray. This confirmed the relative and absolute stereochemistry and revealed that the additions indeed occurred with inversion at the boron-bearing carbon.

Table 2.

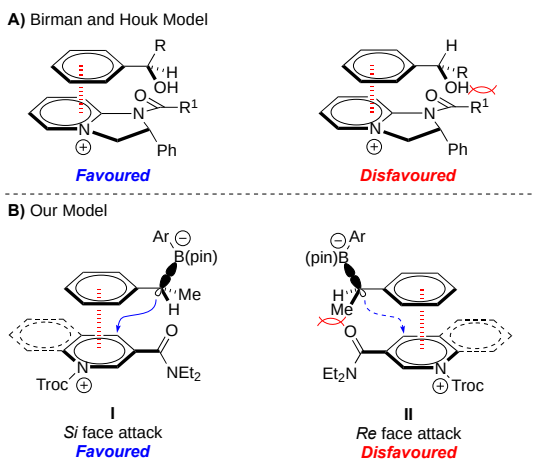


In the case of pyridine **7** the products were again formed with very high levels of diastereoselectivities and complete enantiospecificity. Changes in both the aryl and the alkyl group of the boronic esters were well tolerated and only a slight decrease in diastereoselectivity was observed when the more sterically demanding *i*-Pr group was present on the boronic ester (compound **10c**). The presence of both EDG (*p*-OMe) and EWG (*p*-Cl) on the Ph ring of the boronic ester were evaluated and again resulted in high levels of selectivity (compounds **10d** and **10e**). The use of 3-carbomethoxy substituted pyridine **8** gave the desired product **11a** in high yield and 100% es but lower dr (89:11), as expected.

Rationalisation of the stereochemical outcome.

We rationalise the high levels of stereocontrol in these nucleophilic additions according to the models shown in Scheme 2B. We propose that a strong cation-π interaction between the incoming electron-rich BAC and the electron-deficient quinolinium (or pyridinium) ion should direct the approach of the nucleophile.[17] This dominant interaction leads to the differentiation between the quinolinium (or pyridinium) ion faces due to sterics. Thus, attack on the *Re* face (**II**) would suffer from non-bonded interactions between the amide carbonyl group and the BAC methyl group. This steric congestion will not be present on the *Si* face (**I**) where the smaller H atom is in close proximity to the amide group and so is favoured. It is not clear why the isopropyl substrate **4c** gave lower dr since increased steric repulsion was expected to lead to increased selectivity. Attempts were made to verify the importance of cation-π interactions by testing non-benzylic boronic esters. Unfortunately, dialkyl chiral secondary boronic ester ate complexes were not sufficiently reactive with both the pyridinium and quinolinium salts and simply resulted in oxidation of the boronic ester.

The type of cation-π interactions proposed here is well documented in the literature. In particular, and most relevant here, similar recognitions have been reported by Briman,[18] Houk[19] and Carbery[20] during their development of chiral DMAP-based catalysts for the kinetic resolution of secondary benzylic alcohols (Scheme 2A). In these cases strong, attractive cation-π interactions dominate and the selectivity is determined by steric interactions between the R substituent of the alcohol and the R^1 acyl substituent. These related literature examples provide a solid foundation to our model and highlight the importance of the carboxylic amide on the *C*-3 of the heterocyclic scaffolds as a crucial element for efficient stereocontrol.

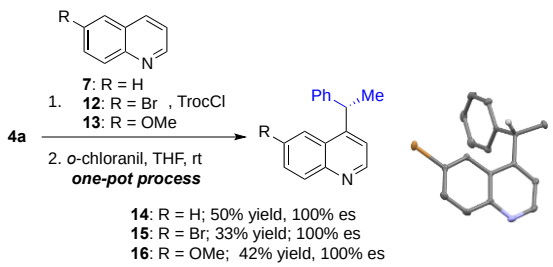


Scheme 2.

Synthesis of Chiral Quinolines

Because quinolines constitute the core of many biological molecules, we reasoned that the installation of chiral groups on

specific position of the intact heterocyclic ring would be very valuable.[1] Thus, a two steps sequence of [1,4]-addition–oxidation was attempted. As described in Scheme 2, addition of BAC (*R*)-**4a** [er (*R*:*S*) 95:5] to commercially available quinolines **7**, **12** and **13** gave after oxidation with *o*-chloranil the enantioenriched 4-substitued quinolines **14**–**16** without loss of enantiopurity. Compound **15** was crystallised from Et_2O/pentane providing good quality crystals for X-ray thus confirming the absolute stereochemistry (Scheme 3).



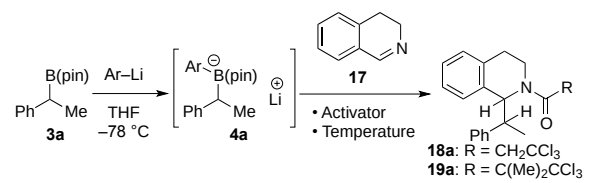
Scheme 3.

Additions to Dihydroisoquinolines

Teytrahydroisoquinolines (THIQs) are very important due to their presence in the structure of many natural products and pharmaceutical compounds.[1] A key feature of this class of molecules is the presence of a substituent at the C-1 position of the heterocyclic ring.[3,8] The development of methods able to control the formation of this stereogenic centre has been the subject of great interest. Thus, we also decided to evaluate the reactivity of our chiral BACs in the context of nucleophilic addition to dihydroisoquinolines.

As reported in Table 3, direct exposure of **15** and Troc-Cl to BAC **4a** [Ar = *p*-OMePh] gave the desired product **18a** in 35% yield and promising 82:18 dr favouring the *anti* diastereomer (entry 1).[21] Based on our previous findings, we decided to employ the electron deficient 3,5-$(CF_3)_2$Ph group in the BAC (entry 2). Surprisingly this modification completely decreased the reactivity of **4a** and no product could be detected, so alternative aryl groups were explored. Pleasingly, when Ph–Li was added to **3a**, the product was obtained in an improved 43% yield and similar level of selectivity (entry 3). In order to enhance diastereoselectivity through non-bonded interactions we sought an even bulkier activator. The use of dimethyl-TrocCl was therefore explored and proved ideal, giving THIQ product **19a** in 70% yield and improved 93:7 dr (entry 5).

Table 3.

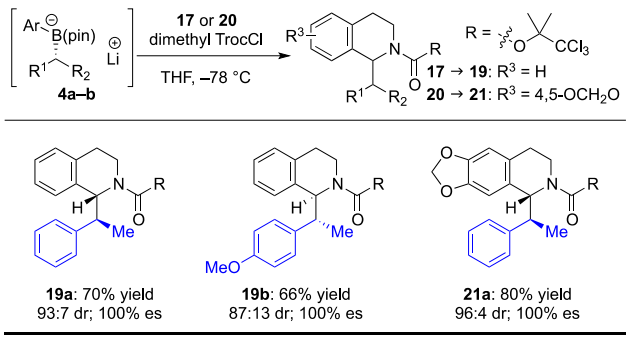


Entry	Ar–Li	Activator	T (°C)	Yield (%)[a]	dr (*syn*:*anti*)[b]
1	*p*-OMePh–Li	TrocCl	–78	35	82:18
2	3,5-$(CF_3)_2$Ph–Li	TrocCl	–78	–	–
3	Ph–Li	TrocCl	–78	43	82:18
4	*p*-OMePh–Li	dimethyl-TrocCl	–78	63	90:10
5	Ph–Li	dimethyl-TrocCl	–78	70	93:7

a) Yields after column chromatography. b) Determined by chiral HPLC on the crude.

The superior levels in terms of efficiency and selectivity prompted us to us to select these reaction conditions for further substrate screening. As revealed in Table 4, this new diastereoselective addition could be adapted to various enantioenriched BACs (**4a**,**b**) and dihydroisoquinolones (**17**, **20**). In all cases the expected products **19a**,**b** and **21a** were formed in good yields and excellent to good diastereoselectivities and complete enantiospecificities (with inversion).

Table 4.



Conclusions

In conclusion, we have developed new diastereoselective additions of chiral "boron-ate" complexes derived from enantioenriched secondary boronic esters to quinolinium, pyridinium and dihydroisoquinolinium ions. Our method furnishes enantioenriched heterocyclic structures with very high diastereocontrol over two contiguous stereogenic centres and with very high enantiocontrol. The unusually high diastereoselectivity observed is thought to originate from strong cation-π interactions between the cationic heterocycle and the electron rich benzylic boronate complex with minimisation of steric interactions between the substituents on the ate complex and the non-planar substituents on the heterocycle. Given the relevance of these heterocyclic scaffolds in natural product synthesis and pharmaceutical chemistry, the methodology should find broad applicability. In addition, we have demonstrated the further potential of chiral "boron-ate" complexes as a useful and readily available class of chiral nucleophiles. Further extension of this chemistry towards the total synthesis of a range of biologically active alkaloids is currently underway in our laboratories.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Detailed experimental procedures and spectrospic data for all new compounds. X-Ray data analysis for compounds **9e**, **15** and **19a**. See DOI: 10.1039/b000000x/

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15 The lower dr observed is likely to be due to the increased planarity of the ester with the heterocycle. This will reduce the steric interactions between the nucleophile and substituents thereby leading to lower dr.

16 For the preparation of the enantioenriched boronic esters **3a**–**e**, see the Supporting Information.

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21 The relative stereochemistry of racemic **16a** (R = Troc) has been determined by Troc-deprotection to give **19** and X-Ray analysis of the hydrochloride salt (See SI).